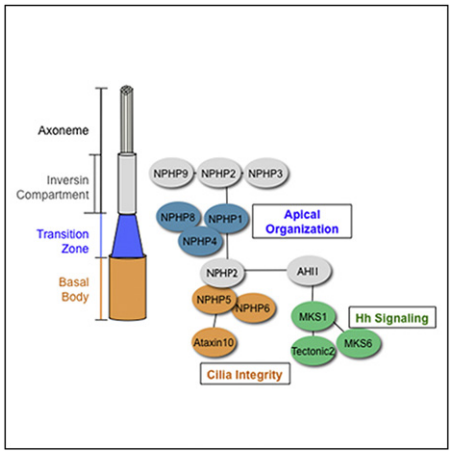
In This Issue

Cell



Parsing Ciliopathies with Proteomics

PAGE 513

Ciliopathies are often defined as distinct syndromes, but they share overlapping phenotypes such as cystic kidneys, retinal degeneration, and neural tube malformation. Sang et al. used a proteomic approach to parse the relationship between these different symptoms and specific cilia-related processes, such as cell polarity and signaling. Mapping the interaction network between proteins involved in several ciliopathies revealed three connected modules each involved in a particular attribute of ciliopathies. Moreover, proteins detected in the interaction network led to the identification of two new disease genes.

A Fork in the Road for BRCA2

PAGE 529

The breast cancer suppressor BRCA2 is critical for repair of DNA double-strand breaks via homologous recombination. Schlacher et al. now show that BRCA2 also prevents these lesions from occurring at stalled replication forks by stabilizing RAD51 nucleoprotein filaments that protect newly synthesized DNA strands from nuclease-mediated degradation. These findings reveal an unexpected role for BRCA2 in maintaining genomic integrity and suggest a novel mechanism of tumor suppression.

Balancing Act for Chromatin States

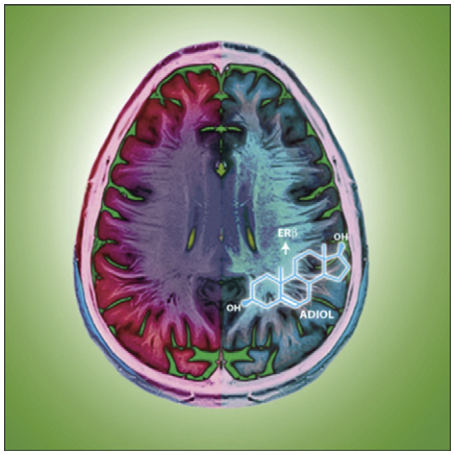
PAGE 543

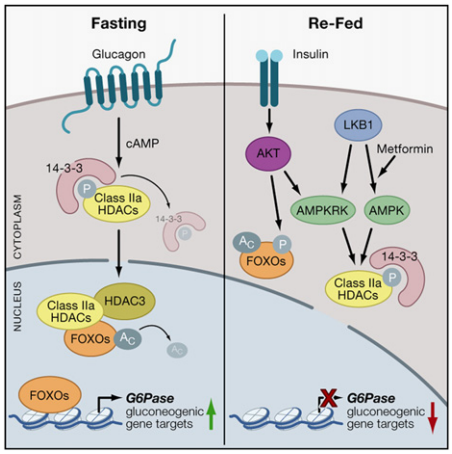
Cells maintain a constant ratio of silent and active rRNA genes. Wittner et al. now show that the balance of open and closed chromatin states at yeast rRNA genes results from a dynamic equilibrium between transcription-dependent removal and replication-dependent assembly of nucleosomes, as opposed to stable, inheritable chromatin states at individual loci. Thus, the opposing effects of replication and transcription can reset chromatin states during each cell cycle.

A-DIOL-Down for Multiple Sclerosis

PAGE 584

Microglia control inflammatory responses in the brain, but deregulation of this response often contributes to neurodegenerative diseases, including multiple sclerosis (MS). Now, Saijo et al. discover an endogenous pathway in microglia, anchored by the estrogen receptor β (ERβ), which suppresses neuroinflammation and can inhibit pathologies similar to MS in a mouse model of the disease. Specifically, the ERβ ligand ADIOL triggers the recruitment of the corepressor complex CtBP to AP-1-dependent promoters, thereby repressing genes that amplify inflammatory responses and activate pathogenic T cells.





HDACs Make Gluconeogenesis FOX-y

PAGE 607 and PAGE 596

During fasting, the insulin-regulated transcription factor FOXO maintains energy balance by triggering the expression of catabolic genes. Mihaylova et al. and Wang et al. now identify class IIa histone deacetylases (HDACs) as conserved hormone-inducible FOXO coactivators. In the *Drosophila* fat body and the mammalian liver, class IIa HDACs translocate to the nucleus in response to hormonal signaling and deacetylate FOXO to promote transcription. Liver-specific depletion of these HDACs reduces blood sugar levels in mouse models of type II diabetes, suggesting a potential role for HDAC inhibitors as therapies for metabolic disease.

A Chromatin Lock on Olfactory Receptors

PAGE 555

Olfactory receptor (OR) genes are transcribed in a monogenic, monoallelic fashion so that each neuron expresses only one of several thousand alleles. Here, Magklara et al. show that chromatin-mediated silencing—trimethylation of histones H3K9 and H4K20—establishes the foundation for this selective regulation. The authors show that silencing is established prior to OR transcription. The findings indicate that heterochromatin marks typically thought to be static are reversed to allow expression of one OR per neuron.

p53 Targets: Not the Usual Suspects

PAGE 571

p53 launches transcriptional programs to both stimulate DNA damage repair and suppress uncontrolled growth. Brady et al. show that these functions of p53 are distinct, as alleles of p53 that compromise the DNA damage response do not affect p53-mediated tumor suppression. Surprisingly, most of the annotated p53 target genes are dispensable for tumor suppression, and the authors identify a small set of previously unrecognized p53 target genes associated with its tumor suppressor function. The findings may inform therapy designed to block p53-dependent side effects of chemotherapy without impacting p53 tumor suppression.

A Hot Flash for Estrogen

PAGE 622

Hah et al. characterize the immediate effects of estrogen signaling on the transcriptome of breast cancer cells. By detecting nascent transcripts, the authors find that estrogen regulates a quarter of the transcriptome in a rapid, robust, and unexpectedly transient manner. Estrogen targets include both protein-coding and noncoding transcripts and many previously unannotated intergenic transcripts. The results provide a comprehensive view of the primary transcriptional effects of estrogen and a model for studying rapid signal-dependent transcription in other systems.